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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/543,371	KALLURI, RAGHURAM	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 1/7/04, is acknowledged.

2. Claims 1-4 and 9 are pending and under consideration in the instant application.

3. In view of the amendment filed on 1/7/04, only the following rejections are remained.

4. The specification on page 125, Table 2 is objected to because the amendment, filed 11/11/02, to the drawing of Figure 18B and change SEQ ID NO: 10 from 245 to 244 amino acids in length is not reflected on Table 2. Table 2 provides the fragments length based on the SEQ ID NO: 10 as originally filed (245aa). For example Tum-4 as originally filed is aa 181-244, however after the amendment to Figure 18B and the SEQ ID NO: 10, the amino acid of Tum-4 should be 180-243 because the amendment to Fig 18B/SEQ ID NO: 10 deleted the first amino acid of the sequence. These changes should be also reflected on the Table 2 and claims. For example claim 9.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, and 9 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a non-Goodpasture fragment of α3(IV) NC1 domain consisting of amino acid residues 185-203 of SEQ ID NO: 10, having at least one of the following activities (a) the ability to bind αvβ3 integrin, and the ability to inhibit proliferation of melanoma cells in vitro, wherein the ability to bind αvβ3 integrin is RGD-independent, an isolated fragment of α3(IV) NC1 domain, consisting of the amino acid sequence of amino acid residues 53-123 of SEQ ID NO:10, an isolated fragment of α3(IV) NC1 domain, consisting of the amino acid sequence of amino acid residues 181-244 of SEQ ID NO:10, does not reasonably provide **enablement** for a composition a non-Goodpasture fragment of α3(IV) NC1 domain and "comprising" amino acid residues 15 of SEQ ID NO:10, having at least one of the following activities (a) an ability to bind αvβ3 integrin and (b) an ability to inhibit proliferation of tumor cells *in vivo*, and a pharmaceutically-acceptable carrier in claims 1, wherein the ability to bind αvβ3 integrin is RGD-independent in claim 2, wherein the tumor cells are melanoma cells in claim 3, an isolated fragment of α3(IV) NC1 domain, "having" the amino acid sequence of amino acid residue 53 to amino acid 123 of SEQ ID NO:10 in claim 4; an isolated fragment of α3(IV) NC1 domain, "having" the amino acid sequence of amino acid residue 180 to amino acid residue 245 of SEQ ID NO: 10 in claim 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 7/7/03.

Applicant's arguments, filed 1/7/04, have been fully considered, but have not been found convincing.

Applicant argues that although the Examiner is correct that the terms "comprising" and "having" are open ended and can include additional residues, all of the claims as written are directed to an isolated fragment of a3(1V) NCI domain (or a composition comprising a fragment) having a specific, recited amino acid sequence as set forth in SEQ ID NO:10. As demonstrated in the examples of the specification, the inventor has discovered that this particular amino acid sequence contains the binding site for αvβ3 integrin, as well as the disclosed biological activities, including the ability to inhibit proliferation of tumor cells. Applicant submits that the claims **as written do not include structural changes or modifications, and thus all non-Goodpasture fragments falling within the scope of the claims will have the recited activity**. No additional experimentation is required to practice the claimed invention.

Contrary to applicant assertion that the claims as written do not include structural changes, or modification, the claims as written using open ended language that open up the fragments to include amino acids on either or both sides of the N- terminal or C-terminal and as such this is consider as a change in the amino acid structure. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. A person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the ability to inhibit proliferation of tumor cells and to bind αvβ3 integrin, other than the amino acid residues 185-203, 53-123 and 181-224 of SEQ ID NO:10.

Regarding the pharmaceutical composition, Applicant submits that the operability of the claimed non-Goodpasture fragments of α3(IV) NCI domain is not at issue. The examples show that the non-Goodpasture fragment of α3(lV) NCI domain having amino acid residues 185-203 and 181-244 of SEQ ID NO:10 (claims 1 and 9, respectively) have the ability to bind αvβ3 integrin and inhibit proliferation of tumor cells. Applicant contends that it is well established law that if a compound itself is shown to have the disclosed activity (i.e., is operative or enabled), then compositions comprising the compound are similarly enabled. For example, in *In re* Bundy, 209 U.S.P.Q. 48, 51-21 (CCPA 1981), the court ruled that applicant's disclosure was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possessed activity similar to known prostaglandins. Applicant submits that the present case, not only does the specification provide evidence that the disclosed non-Goodpasture fragments have certain pharmacological properties, but it also (unlike the specification in Bundy) provides specific dosages and protocols for using compositions comprising the fragments (see, e.g., page 67, line 8, through page 70, line 22). Thus, Applicant respectfully submits that the specification provides enabling support for claims 1-4 and 9.

However, In Brana, the court further pointed out that the purpose of treating cancer with chemical compounds does not suggest, per se, an incredible utility. Where the prior art disclosed "structurally similar compounds to those claimed by applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models . . ., one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face." 51 F.3d at 1566, 34 USPQ2d at 1441. In the instant case the specification does not provide an effective chemotherapeutic *in vivo* data of either the claimed non-Goodpasture fragments of α3(IV) NCI domain or structurally similar compounds to non-Goodpasture fragments of α3(IV) NCI domain. One skilled in the art would not know how effectively use the pharmaceutical composition as claimed.

Regarding the unpredictability of adhesion-based therapy, Applicant points out that the cited reference, published in 1992, is not an accurate representation of the state of the art at the time the present application was filed (April 2000). Moreover, Applicant argues that the claims are directed to isolated fragments of non-Goodpasture fragments of α3(IV) NCI domain having demonstrated biological activity and compositions comprising these fragments, not methods for treating adhesion-based disorders based on generalized principles, as discussed in the Edgington reference. Thus, Applicant submits that the Edgington reference is irrelevant to the issue of enablement of the present invention.

Contrary to Applicant assertions, Edgington is still relevant to the enablement of the claimed fragments of non-Goodpasture fragments of α3(IV) NCI domain because the specification does not provide an *in vivo* clinical setting for initial evaluation for the claimed composition.

Regarding Kogan et al., J Biol. Chem. (1995) Applicant argues that none of claims 1-4 or 9 recite fragments of l3(IV) NCI domain comprising structural changes or modifications, but rather are directed to specific, recited amino acid sequences of SEQ ID NO:10. Thus, Applicant submits that the Kogan et al. reference is also irrelevant to the issue of enablement of the present invention.

Contrary to Applicant assertions, the open ended language used in the claims open the recited fragments to include undisclosed amino acids on either or both sides of the N-terminal or C-terminal of the fragments. Such insertion and addition of amino acids to the fragments mount to a change in the length of the recited fragments. Therefore, Kogan et al is applicable to the issue at hand.

7. As stated in the previous office actions mailed on 06/05/01, 3/12/02 and 7/7/04, the filling date of claims with limitation which include the α3(IV) NC1 domain of Collagen from amino acids 53-123 and 185-203, of claims 1-4, is deemed to be the filling date of the instant application, filed 4/4/00, as no support is found for the said polypeptide fragments in priority documents 60/126,175 , 60/089,689 or 09/335,224.

Applicant submits that the claims as currently pending are implicitly or inherently supported in the earlier filed applications. U.S. App. No. 09/335,224 has an identical counterpart International Application, which published as WO 99/65940. Applicant submits that one of ordinary skill, upon reading that disclosure, would have all of the information needed to isolate and assay additional anti-angiogenic fragments, including those disclosed in the present application. Moreover, according to the Examiner's reasoning, anyone can use the teachings of WO 99/65940 to isolate anti-angiogenic fragments. Thus, according to the Examiner's own logic, the fragments of the present invention are inherently supported by the previous filings. If that were not the case, then one of skill in the art, based on the teachings of WO 99/65940, could not arrive at the claimed invention. Applicant therefore respectfully requests that the refusal of priority on these grounds be reconsidered and withdrawn.

However, the introduction of claim changes which involve narrowing the claims by introducing a specific core structure for anti-tumor which are not supported by the priority applications disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalluri *et al* (J Biol Chem. 271(15):9062-9068, 1996) (IDS Ref. No. AW) for the same reasons set forth in the previous Office Action mailed 7/7/03.

Applicant's arguments, filed 1/7/04, have been fully considered, but have not been found convincing.

Applicant points out that the cited Kalluri reference, which is the inventor's own work, does not disclose the composition of claims 1-4. Specifically, nowhere in that reference is there any teaching or suggestion of combining an isolated non-Goodpasture fragment with a pharmaceutically acceptable carrier, as required by amended claim 1. Rather, the cited reference describes inhibition ELISA experiments using α3(IV) NCI mutants in serum. Applicant submits

that serum is not considered a pharmaceutically acceptable carrier. Serum is known to carry a variety of potentially fatal viruses and prions, including viruses such as Hepatitis C, HIV, etc., and many other known and/or as of yet unidentified pathogens.

However, the specification on pages 124-128 uses the claimed fragments of claims 1-4 and 9 in a media that must contains serum. Specially, because the proliferation of endothelial cells (C-PAE cells) and WM-164 melanoma cells requires serum. Therefore, the reference teachings is in agreement with the specification teachings with respect to the composition.

10. Claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by Han *et al* (J Biol Chem. 272(33):20395-20401, 1997) (IDS Ref. No. AT4) for the same reasons set forth in the previous Office Action mailed 7/7/03.

Applicant's arguments, filed 1/7/04, have been fully considered, but have not been found convincing.

Applicant argues that nowhere in the cited reference is there any teaching or suggestion of combining an isolated non-Goodpasture fragment with a pharmaceutically acceptable carrier, as required by independent claim 1. Applicant submits that conditioned medium taught by Han *et al* is not considered a pharmaceutically acceptable carrier.

However, the specification on pages 124-128 uses the claimed fragments of claim 1 in a media. Therefore, the reference teachings is in agreement with the specification teachings with respect to the composition.

11. Claims 1-4 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S Patent No. 5,973,120 (IDS Ref. No. AJ) for the same reasons set forth in the previous Office Action mailed 7/7/03.

Applicant's arguments, filed 1/7/04, have been fully considered, but have not been found convincing.

Applicant submits that nowhere in this reference is there any teaching or suggestion of combining an isolated non-Goodpasture fragment with a pharmaceutically acceptable carrier, as required by Applicant's claims. Applicant submits that the cited reference describes inhibition ELISA experiments using antisera âom two Goodpasture (GP).

However, the specification on pages 124-128 uses the claimed fragments of claims 1-4 and 9 in a media that contains antibodies (anti-Tum-4). Therefore, the reference teachings is in agreement with the specification teachings with respect to the composition.

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
March 14, 2004

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